A Physiological-based Pharmacokinetic (PBPK) Modeling Approach to Quantifying Drug-Drug Interactions: Applications to the Development of Fenfluramine (ZX008) for Treatment of Seizures in Dravet Syndrome (DS)

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INTRODUCTION

• Dravet syndrome (DS) is a severe form of childhood epilepsy in which seizures are often refractory to traditional antiepileptic drugs (AEDs).
• Low dose fenfluramine (ZX008; Zogenix, Inc.) has shown promise in DS patients and is currently under development as adjunctive therapy (top dose of 0.8 mg/kg/day, max of 30 mg/d), including combination with stiripentol/clobazam/valproic acid (STP/CLB/VPA) worldwide.
• Treatment of DS patients often requires a regimen of several AEDs that are metabolized via CYP450, which might result in drug-drug interactions (DDI).

METHODS

• Study 1505 Design
  - Phase 1, single dose, three-way crossover study in healthy adults (N=20)
  - Study arm (17 days wash out period):
    - a. ZX008 0.8 mg/kg;
    - b. STP 3500 mg / CLB 20 mg / VPA 25 mg/kg (max 1500 mg);
    - c. ZX008 0.8 mg/kg + STP 3500 mg / CLB 20 mg / VPA 25 mg/kg (max 1500 mg);
• Draft, pre-lock PK data were available at the time of this study.

RESULTS

• Monotherapy model
  - Fenfluramine (FEN) PBPK model comprised of ten perfusion-limited tissues.
  - Drug-drug interaction models
    - The DDI model predicted the mean AUC0-72 of FEN elevated 1.67-fold after in conjunctive with STP/CLB/VPA, suggesting that the DDI between FEN and STP/CLB is modest in healthy adults.
  - The DDI model predicted the mean AUC0-72 of STP/CLB/VPA to marginally increased in patients with renal impairment, suggesting that FEN dose adjustment might not be warranted in these sub-populations.
  - Model simulations suggest that FEN/norFEN exposure would be marginally increased in patients with renal impairment, qualifying the robustness of this model.

CONCLUSIONS

• PBPK modeling the DDI between FEN and STP/CLB has been developed in healthy adults. The model predicted changes of FEN/norFEN exposure after combination treatment were in good agreement with clinical observations, qualifying the robustness of this model.
• The DDI model predicted the mean AUC0-72 of STP/CLB/VPA are not significantly impacted by the co-administration of FEN in healthy adults.
• Model simulations suggest that FEN/norFEN exposure would be marginally increased in patients with renal impairment, suggesting that FEN dose adjustment might not be warranted in these sub-populations.
• This model can be further extrapolated to quantify potential DDIs and to facilitate dose justification for clinical trials of ZX008 in pediatric patients with DS.

REFERENCES